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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:	WO 91/08200
C07D 211/70, A61K 31/44	A1	(43) International Publication Date:	13 June 1991 (13.06.91)

(21) International Application Number: PCT/HU90/00076

(22) International Filing Date: 22 November 1990 (22.11.90)

(30) Priority data:
6335/89 1 December 1989 (01.12.89) HU

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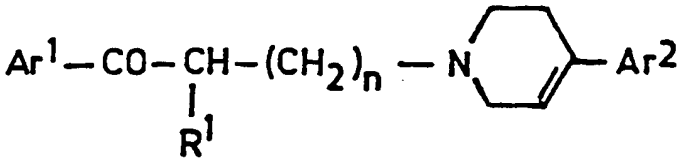
(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), SU, US.

Published
With international search report.

(54) Title: NOVEL TETRAHYDROPYRIDINE DERIVATIVES, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS AS ACTIVE AGENTS



(I)

(57) Abstract

The invention relates to novel tetrahydropyridine derivatives, a process for their preparation and pharmaceutical compositions containing such compounds as active agents. In formula (I), Ar^1 means a phenyl group optionally mono- or polysubstituted, Ar^2 means a phenyl group optionally substituted, R^1 means a hydrogen atom or an alkyl group with 1-6 carbon atoms, n can be either 0 or 1 with the proviso that if n = 0 then R^1 can only mean a hydrogen atom and Ar^2 is in any case substituted.

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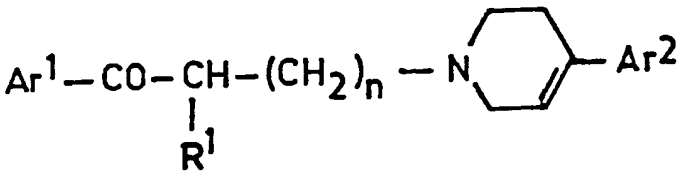
NOVEL TETRAHYDROPYRIDINE DERIVATIVES, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING SUCH COMPOUNDS AS ACTIVE AGENTS

This invention relates to novel tetrahydropyridine derivatives, a process for their preparation and pharmaceutical compositions containing such compounds as active agents.

The compounds of the invention are characterized by formula (I),



(I)

in which

Ar^1 means a phenyl group optionally mono- or polysubstituted,

Ar^2 means a phenyl group optionally substituted,

R^1 means a hydrogen atom or an alkyl group with 1-6 carbon atoms,

n can be either 0 or 1 with the proviso that if n = 0 then R^1 can only mean a hydrogen atom and Ar^2 is in any case substituted.

The compounds of formula (I) are active biologically and possess with a significant nootropic effect.

Ar^1 and Ar^2 groups are either phenyl or substituted phenyl groups.

Phenyl groups can be mono- or polysubstituted with halo, trifluoromethyl, hydroxy, alkyl with 1-6 carbon atoms and alkoxy with 1-6 carbon atoms.

Halo is generic to fluoro, chloro, bromo or iodo.

Alkyl groups as such or as a part of other groups are straight and branch chained saturated hydrocarbon groups such as methyl-, ethyl-, n-propyl-, isopropyl-, n-butyl-, sec-butyl-, n-pentyl-, isopentyl, n-hexyl, isohexyl and the like.

Compounds of formula (I) can be regarded as α- or β--aminoketones, depending on the value of n where the nitrogen atom is the heteroatom of the substituted tetrahydropyridine cycle.

β-amino ketones, which are also called as Mannich ketones, are well known. Their chemical characteristics are described, for example, in F. F. Blicke: Organic reactions, Vol. 1, p. 303-341, J. Wiley, New York, London (1942); B. Reichert: Die Mannich-Reaktion, Springer Verlag, Berlin, Göttingen-Heidelberg, (1959); H. Hellmann - G. Opitz: α-Aminoalkylierung, Verlag Chemie, Weinheim/Bergstr. (1960).

Types of compounds described on this field up to now are highly diversified, number of factual compounds is very high. From medical point of view more significant β-ketones are e. g. propipocain hydrochloride [3-(1-piperidinyl)-1-(4-propoxy-phenyl)-1-propanone] known as local anaesthetic from the DD (East-German) patent specifications Nos. 9330 and 9565 and tolperison hydrochloride [2-methyl-1-(4-methyl-phenyl)-3-(1-piperidinyl)-1-propanone] as vasodilator or central muscle relaxant known from the Hungarian patent specification No.

114,997. Here can be mentioned the coronary effective oxyphedrine hydrochloride /-R(R*, S*)-3-(2-hydroxy-1-methyl-2-phenylethyl)-amino-1-(3-methoxyphenyl)-1-propanone/ which is described in the DE patent specification No. 1,439,574 and the α-receptor blocking agent 6-/-3-(3-phenylpyrrolidinyl-propionyl/-benzodioxane described in DE A-2,252,344.

U. S. patent specification No. 3,426,036 describes, together with some other compounds, β-amino ketones in the case of which the tetrahydropyridine ring contains the nitrogen atom as a ring member. These compounds have muscle relaxant effects.

Tetrahydropyridine compounds, which can be considered as α-amino ketones, are discussed by M. Rajsner, E. Adlerova and M. Protiva in Collection Czechoslov. Chem. Communs. 28. 1031-43 (1963), however, the analgetic effect mentioned in said article is not proven for compounds containing a tetrahydropyridine cycle.

M. Celadnik, K. Palát, A. Sehere and C. Vrba describe tiomorpholinyl substituted two β-amino ketones in Arch. Pharm. 291 : 3 (1958). Both compounds are mentioned as local anaesthetics in said publication.

Among the γ-amino ketones which are similar in structure to compounds of formula (I), 4-/-4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl/-1-(4-fluorophenyl)-1-butanone with neuroleptic activity can be mentioned, said compound is also known as haloperidol but also a high number of its structural analogues are known. Another member of this group is a hypertension reducing agent, known as pitenodil with the chemical name 2-/-4-

-(3-(tenoyl)-propyl)-1-piperazinyl]ethyl dimethyl carbamate.

DE patents Nos. 865,314 and 870,700 describe a γ-amino ketone type compound which is a well known analgetic under the name methadon and its chemical name is 6-(dimethylamino)--4,4-diphenyl-3-heptanone.

The compounds of the formula (I) are, however, nootropic agents, they are protecting cerebral activity from several harmful effects, like hypocrisy, having a damaging influence on the cognitive functions.

This effect is shown by controlling amnesia, caused by hypocrisy.

Male, spontaneous hypertensive rats weighing between 190 and 220 grams (average blood pressure is about 180-220 mmHg) are trained in conditioning boxes, so-called shuttle boxes, consisting of two parts, to form two way active preventing reaction. The animals performed 30 cycles per day which consist of 15 sec intersignal relaxation time, 15 sec light stimuli (conditioned stimulus: flashing light signal of 1 Hz frequency) and 10 sec electrical shock (unconditioned stimulus: 0.8 mA electrical shock through the foot grid). Shocking effect can be avoided if animals change their area under light stimulus, hence a conditioned protective reaction is shown. Animals were conditioned for 3 days.

On the 4^{th} day, animals (n=6) were treated by 10.0 mg/kg of the test compound (5 ml/kg in volume) orally. A control group (n=6) was treated by two solvents, one under normal normoxic conditions, the other under hypoxic conditions completes 30 cycles at the fourth day (normoxic and hypoxic

controlls, respectively). 60 minutes after pretreatment either with a solvent or with a compound to be tested, animals are put to a shuttle box, where nitrogen enriched compressed air is flown (200 litres per minute per box) and during 10 minutes, the oxygen content of inspired air is reduced to 6 per cent. After equilibrum animals perform 30 cycles under hypoxic conditions.

The number of conditioned reactions is registered by a microprocessor controlled system automatically. From the number of conditioned reactions given by the animals the average of groups can be computed. Antihypoxic effect of compounds to be tested, expressed in percentage, can be computed by the formula shown below:

$$\frac{C - B}{A - B} \times 100$$

where

A = average of conditioned preventing reactions in normoxic control group on the 4^{th} day

B = average of conditioned preventing reactions in hypoxic control group on the 4^{th} day

C = average of conditioned preventing reactions on the 4^{th} day of the group treated orally with 10.0 mg per kg of the compound to be tested.

Effect on memory damage caused by hypoxia and acute toxicity data of certain representives of the compounds of formula (I) are given in Table I.

Table I

No. of the preparation example of the active agent	Dose (mg/kg) p.o.	Protecting effect to amnesia (%)	LD_{50} (mg/kg)
1	10.0	60	>2000
27	10.0	54	>1000
11	10.0	51	1150
14	10.0	83	1200
16	10.0	50	>1000
17	10.0	54	850
10	10.0	67	>2000
21	10.0	64	>2000
Vincamine (reference)	10.0	24	760
Naphthidrofuryl (reference)	100.0	0	-
Piracetam (reference)	100.0	71	>2000
	10.0	0	

A general characteristic of the so-called cognitive stimulants that they are capable to protect the upper nervous system from several harmful agents. Normobaric hypoxia used in the described tests serves modelling such human conditions in which cognitive functions caused by disturbance in circulation and metabolic poblems, like supply troubles in old age, are getting worse.

Reference materials used in our trials are used in broad

scale in old age or other amnesia therapy. Vincamine and Naphthidrofuryl are affecting their advantageous influence by the stimulation of cerebral vasodilatation and cerebral metabolism.

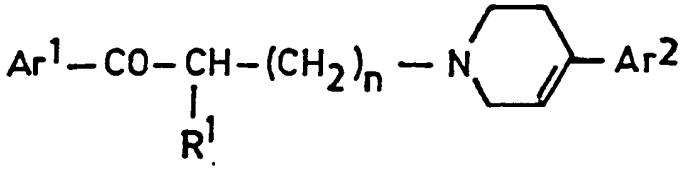
In the normobaric hypoxy model used by us, Vincamine as reference material shown a limited effect at a dose of 10.0 mg per kg, 100.0 mg per kg of Naphthidrofuryl was also ineffective, similar to 10.0 mg/kg of Piracetam which was effective only at a concentration of 100 mg per kg.

The compounds, according to the invention provide, however, considerable protection against amnesia at an oral dose of 10.0 mg per kg; therefore they are proven as being more effective materials than those which are used extensively in human therapy.

Toxicity tests were completed with mice having weights between 19 and 21 grams. Test materials have been added by stomach tube in volume of 0.1 ml per 10 g body weight. LD_{50} values are calculated according to Litchfield-Wilcoxon.

As it is seen from the data of Table I, the compounds according to the invention possess an acceptable therapy range when added orally.

The new tetrahydropyridine derivatives of the formula (I)



(I)

in which

Ar^1 means a phenyl group optionally mono- or polysubstituted,

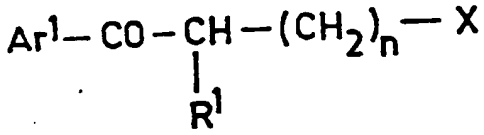
Ar^2 means a phenyl group optionally substituted,

R^1 means a hydrogen atom or an alkyl group with 1-6 carbon atoms,

n can be either 0 or 1 with the proviso that if n = 0 then R^1 can only mean a hydrogen atom and Ar^2 is in any case substituted

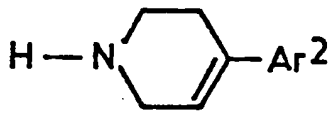
and their acid addition salts can be prepared e. g. as follows:

a) a ketone of the formula (II)



(II)

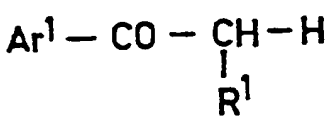
in which Ar^1, R^1 and n are as defined above and X means a halogen atom, is reacted with a substituted tetrahydropyridine derivative of the formula (III)



(III)

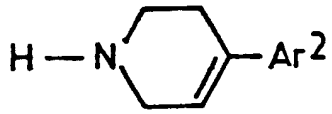
in which Ar^2 is as defined above, or

b) a ketone of the formula (IV),



(IV)

in which Ar^1 and R^1 are as defined above, is reacted with a tetrahydropyridine derivative of the formula (III),



(III)

in which Ar^2 is as defined above, or its salt and formaldehyde or a formaldehyde source to obtain a compound of the formula (I) with n = 1,

and, if desired, converting a compound of the formula (I), obtained by process a) or b) into an acid addition salt.

Process a) according to the invention is performed suitably by reacting a tetrahydropyridine derivative of the formula (III) in basic form with a halo compound of the formula (II) in a polar solvent, like acetone, ethanol or acetonitrile or their mixtures, in the presence of an acid binding agent, which bonds the acid HX liberated during said reaction. As acid binding agents tertiary amines of low number of carbon atoms, preferably triethyl amine; 1-methylpiperidine, or salts of weaker acids than HX, suitably salts of organic acids, preferably sodium acetate, can be used. When using as starting material a compound of the formula (II) with n = 0 the cooling of the reaction mixture is strongly recommended.

Compounds of formula (I) obtained in basic form can be transformed to a salt, if required.

To form salts both in the case of the compounds of the formulae (I) and (III) most preferable materials are those

mineral acids which can be used to medical purposes. Preferably hydrogen chloride, hydrobromic acid, sulphuric acid and similar acids are used.

In case of compounds of the formula (I), other organic acids, like methanesulphonic acid or fumaric acid, can be also used, mainly to improve water solubility of the target compound.

The raw products can be purified e. g. by recrystallization.

Process b) according to the present invention can preferably be realized so that an aromatic ketone of the formula (IV), in which Ar^1 and R^1 are as defined above, is reacted with paraformaldehyde and a salt of a tetrahydropyridine derivative of the formula (III), in a polar solvent under heating in a condensation reaction. As solvent preferably ethanol or 2-propanol is used. Paraformaldehyde is preferably used in an excess of e. g. 2.5 moles, based on the ketone, and it is given in several portions to the reaction mixture. The depolymerization of paraformaldehyde to formaldehyde can be catalized by an acid, preferably with the acid used for preparing a salt of the tetrahydropyridine of the formula (III).

Paraformaldehyde can be replaced by formaldehyde, preferably in aqueous solution. To provide a homogenous reaction medium, the reaction is performed in the presence of a water soluble organic solvent, preferably ethanol or methanol.

Paraformaldehyde can be also replaced by those compounds which can be transformed during the reaction to formaldehyde and an another compound which does not affect the reaction required. Acetals made from formaldehyde with aliphatic

alcohols of low number of carbon atoms, preferably dimethoxy or diethoxy ethane, meet said requirement. Acetals should be added preferably in several steps to the reaction mixture.

Progress of the reaction can be followed by thin layer chromatography and the optimal reaction time can be determined by this method. Compounds of the formula (I) can be separated by cooling when reaction is completed and this is typical in the most cases. In other cases, crystallization can be promoted by addition of acetone or an other solvent which can be mixed with the used one. From the salt of a final product of the formula (I) of hardly crystallizing character, the free base can be deliberated by treatment with an alkali metal carbonate, e. g. potassium carbonate, in water, the free base can be extracted by an apolar solvent and then, after a usual isolation, be converted to the salt required.

Raw compounds of the formula (I) are recrystallized in a usual manner. It is preferable to use methanol only, or a mixture of methanol and ethanol because by this method the raw product can be separated from the salt of a heterocyclic compound of the formula (III) which is a by-product. Other polar solvents, like acetone or acetonitrile, can be used, naturally.

The homogenity of the end-product can be checked by thin layer chromatography, too.

Starting compounds of the formulae (II) and (IV) are generally known and these compounds can be prepared by usual methods. Tetrahydropyridine compounds of formula (III) are, however, not very well known. These compounds can be prepared

according to the method of US patent specification No. 2,973,363 from alpha-methyl styrene or its derivatives substituted on the benzene ring.

If desired, the compounds according to the invention can be converted into pharmaceutical compositions. These compositions may be administered in oral, rectal and/or parenteral route. For oral administration, the composition may be formulated e. g. as a tablet, dragée or capsule. In order to prepare oral compositions, e. g. lactose or starch may be used as carriers. Gelatine, carboxymethylcellulose sodium, methylcellulose, polyvinylpyrrolidone or starch gum are suitable binding or granulating agents. As disintegrating agents mainly potato starch or microcrystalline cellulose may be added though ultraamylopectin or formaldehyde-casein and the like are also useful.

Talc, colloidal silicic acid, stearin, calcium or magnesium stearate and the like are suitable anti-adhesive and sliding agents.

Tablets may be prepared e. g. by compression following the wet granulation. The mixture of the active ingredient with the carriers and optionally with a part of the disintegrating additive is granulated with an aqueous, alcoholic or aqueous--alcoholic solution of the binding agents in a suitable equipment, then the granulate is dried. Subsequently, after mixing the other disintegrating, sliding and anti-adhesive additives to the dried granulate, the mixture is compressed to tablets. If desired, the tablets may be provided with a groove in order to facilitate the administration. Tablets may also directly

be prepared from a mixture containing the active ingredient and suitable additives. The tablets may optionally be converted to dragées by employing the commonly used pharmaceutical additives, e. g. protective, flavouring or colouring agents such as sugar, cellulose derivatives (methyl- or ethylcellulose, carboxymethylcellulose sodium and the like), polyvinylpyrrolidone, calcium phosphate, calcium carbonate, food dyes, dyeing lacquers, aromatizing agents, iron oxide pigments and the like. Capsulated compositions are prepared by filling a mixture of the active ingredient with the additives into capsules.

For rectal administration, the composition of the invention is formulated as a suppository containing a carrier mass, the so-called "adeps pro suppositorio" in addition to the active ingredient. As carriers, vegetable fats such as hardened vegetable oils, or triglycerides of C_{12-18} fatty acids (preferably the carriers bearing the trade name Witepsol) may be used. The active ingredient is uniformly distributed in the molten carrier mass, then suppositories are prepared by moulding.

For parenteral administration, the composition of the invention is formulated as an injectable solution. For preparing these injectable solutions, the active ingredients are dissolved in distilled water and/or various organic solvents, e. g. glycol ethers, if desired, in the presence of solubilizing agents such as polyoxyethylene sorbitan monolaurate or monooleate or monostearate (Tween 20, Tween 60 or Tween 80), respectively. The injectable solution may further contain various additives (auxiliary agents), e. g. preservatives such as ethylenediamine tetraacetate as well as pH-modifying and

buffering substances or, if desired, a local anaesthetic agent such as lidocaine. Before filling into the ampoules, the injectable solution containing the composition of the invention is filtered and after filling in, it is subjected to sterilization.

Other details of the present invention are illustrated by the following non-limiting examples. Yield values given below relate to substances purified up to constant melting point.

Example 1

4-(4-Chlorophenyl)-1-((4-chlorophenyl)carbonylethyl)--1,2,3,6-tetrahydropyridine hydrochloride

4.28 g (0.022 moles) of 4-(4 - chlorophenyl) - 1,2,3,6-tetrahydropyridine hydrochloride are added to 25 ml of ethanol, then 3.6 g of (0.044 moles) of sodium acetate are added thereto Under continuous stirring 4.9 g (0.024 moles) of 3-chloro-1--(4-chlorophenyl)propane-1-one are added in small portions within one hour to the suspension obtained. After adding the components, the reaction mixture is stirred for additional 3 hours. The reaction mixture is evaporated to dryness and 50 ml of water are added to residue. The mixture is neutralized with sodium hydrocarbonate and shaken with chloroform. After drying the chloroformic phase is concentrated. The residue is dissolved in a few ethanol and made acidic with hydrogen chloride dissolved in ether. Mass of separated crystallic material is 6.0 g. Yield is 68.7 per cent calculated to raw product. After double recrystallization from ethanol, melting point is 204--205 ^{o}C.

Compounds, prepared as described in Example 1, of the

formula (I) in which R^1 is hydrogen and n = 1 if not otherwise indicated, are summarized in Table II.

Table II

No. of the Example	Ar^1	Ar^2	Salt	Melting point °C	Solvent used for recrystallization
2	4-fluorophenyl	4-chlorophenyl	HCl	200	EtOH i-PrOH 1:1
3	phenyl	phenyl	HCl	162	i-PrOH
4	4-ethylphenyl	phenyl	HCl	170	i-PrOH
5	phenyl	4-fluorophenyl	HCl	178	i-PrOH
6	4-ethylphenyl	4-fluorophenyl	HCl	185	i-PrOH
7	4-fluorophenyl	phenyl	HCl	186-187	EtOH
8	4-fluorophenyl	phenyl	HCl	185-186	EtOH
9	4-fluorophenyl	4-fluorophenyl	HCl	191-192	EtOH
10	4-chlorophenyl	4-fluorophenyl	HCl	194-195	EtOH
11	4-ethylphenyl	3-(trifluoromethyl)phenyl	HBr	191	EtOH i-PrOH
12	phenyl	3-(trifluoromethyl)phenyl	HBr	187-187.5	MeOH i-PrOH 1:1
13	4-chlorophenyl	3-(trifluoromethyl)phenyl	HBr	206-207	MeOH
14	4-fluorophenyl	3-(trifluoromethyl)phenyl	HBr	200	MeOH EtOH 2:3
15	4-fluorophenyl	4-methylphenyl	HBr	200-201	MeOH
16	phenyl	4-methylphenyl	HBr	186	EtOH

continued Table II

No. of the Example	Ar^1	Ar^2	Salt	Melting point °C	Solvent used for re-crystallization
17	4-ethylphenyl	4-methylphenyl	HCl	186	i-PrOH
18	phenyl	3-methylphenyl	HCl	174-175	EtOH
19	4-fluorophenyl	3-methylphenyl	HCl	199-201	EtOH
20	4-chlorophenyl	3-methylphenyl	HCl	193-195	EtOH
21[x]	phenyl	4-chlorophenyl	HCl	220-221	EtOH
22[x]	phenyl	3-(trifluoro-methyl)phenyl	HCl	200-202	i-PrOH

[x] n = 0

Abbreviations: MeOH = methanol
EtOH = ethanol
i-PrOH = isopropanol

Example 23

4-Phenyl-1-((3,4,5-trimethoxyphenyl)-carbonylethyl)--1,2,3,6-tetrahydropyridine

0.8 g (0.027 moles) of paraformaldehyde are added to a mixture of 2.93 g (0.015 moles) of 4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride, 3.58 g (0.017 mole) of 3,4,5-trimethoxyacetophenone and 30 cm^3 ethanol and the reaction mixture is boiled. After one hour 0.4 g (0.013 moles) of paraformaldehyde are added and the mixture is boiled for additional 5 hours. Then the reaction mixture is evaporated and 25 ml of water are added to the residue. The aqueous solution is

neutralized with sodium hydrocarbonate and then shaken with chloroform. After drying the chloroformic solution is evaporated, the residue is dissolved in a few ethanol and transformed to hydrochloride salt as described in Example 1.

The precipitated crystals are filtered, the amount of the product is 2.9 g.

Melting point is 188-189 °C after double recrystallization from ethanol.

Yield: 46.3%.

Compounds of formula (I), prepared as described in Example 1, in which n = 1 and R^1 means a hydrogen atom if not indicated otherwise are summarized in Table III.

Table III

No. of the Example	Ar^1	Ar^2	Salt	Melting point °C	Solvent used for re-crystallization
24	4-hydroxyphenyl	4-chlorophenyl	HCl	189-199	MeOH
25	3,4,5-tri-methoxyphenyl	4-chlorophenyl	HCl	194-195	EtOH
26	4-methylphenyl	4-chlorophenyl	HCl	186-187	EtOH
27	3,4,5-tri-methoxyphenyl	4-fluorophenyl	HCl	185	i-PrOH
28	phenyl	3-(trifluoro-methyl)phenyl	HBr	187-187.5	MeOH EtOH 1:1
29	2-fluorophenyl	3-(trifluoro-methyl)phenyl	HBr	167	MeOH

continued Table III

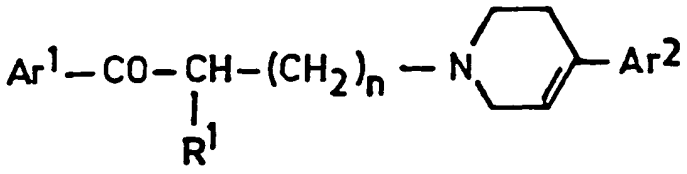
No. of the Example	Ar^1	Ar^2	Salt	Melting point ^oC	Solvent used for re-crystallization
30[x]	3-ethyl-4-fluoro-phenyl	3-(trifluoro-methyl)phenyl	HBr	187	EtOH
31	3,4-dichlorophenyl	4-chlorophenyl	HCl	192-194	EtOH
32	3-methoxyphenyl	4-chlorophenyl	HCl	181-182	EtOH
33	3,4-dimethoxy-phenyl	4-chlorophenyl	HCl	190-191	EtOH

[x] R^1 = methyl group

Abbreviations: MeOH = methanol
EtOH = ethanol
i-PrOH = isopropanol

What is claimed is:

1. New tetrahydro pyridine derivatives of the formula (I)



(I)

in which

Ar^1 means a phenyl group optionally mono- or polysubstituted,

Ar^2 means a phenyl group optionally substituted,

R^1 means a hydrogen atom or an alkyl group with 1-6 carbon atoms,

n can be either 0 or 1 with the proviso that if n = 0 then R^1 can only mean a hydrogen atom and Ar^2 is in any case substituted

and their pharmaceutically acceptable acid addition salts.

2. 4-(4-Chlorophenyl)-1-((4-chlorophenyl)carbonylethyl)-1,2,3,6-tetrahydropyridine,

4-(4-chlorophenyl)-1-(3,4,5-trimethoxyphenyl)carbonylethyl)--1,2,3,6-tetrahydropyridine,

4-(3-trifluoromethylphenyl)-1-((4-ethylphenyl)carbonylethyl)--1,2,3,6-tetrahydropyridine,

4-(3-trifluoromethylphenyl)-1-((4-fluorophenyl)carbonylethyl)--1,2,3,6-tetrahydropyridine,

4-(3-trifluoromethylphenyl)-1-(phenylcarbonylethyl)-1,2,3,6--tetrahydropyridine,

4-(4-methylphenyl)-1-((4-ethylphenyl)carbonylethyl)-1,2,3,6-

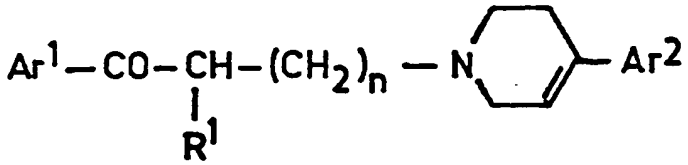
tetrahydropyridine,

4-(4-fluorophenyl)-1-((4-chlorophenyl)carbonylethyl)-1,2,3,6-tetrahydropyridine,

4-(4-chlorophenyl)-1-(phenylcarbonylmethyl)-1,2,3,6-tetrahydropyridine

and their pharmaceutically acceptable acid addition salts.

3. Pharmaceutical composition characterized by containing as active agent a new tetrahydropyridine derivative of the formula (I)



(I)

in which

Ar^1 means a phenyl group optionally mono- or polysubstituted,

Ar^2 means a phenyl group optionally substituted,

R^1 means a hydrogen atom or an alkyl group with 1-6 carbon atoms,

n can be either 0 or 1 with the proviso that if n = 0 then R^1 can only mean a hydrogen atom and Ar^2 is in any case substituted

or its pharmaceutically acceptable acid addition salt.

4. Pharmaceutical composition as claimed in claim 3, characterized by containing as active agent:

4-(4-chlorophenyl)-1-((4-chlorophenyl)carbonylethyl)-1,2,3,6-tetrahydropyridine,

4-(4-chlorophenyl)-1-((3,4,5-trimethoxyphenyl)carbonylethyl)--1,2,3,6-tetrahydropyridine,

4-(3-trifluoromethylphenyl)-1-((4-ethylphenyl)carbonylethyl)--1,2,3,6-tetrahydropyridine,

4-(3-trifluoromethylphenyl)-1-((4-fluorophenyl)carbonylethyl)--1,2,3,6-tetrahydropyridine,

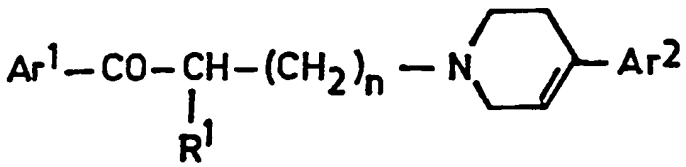
4-(3-trifluoromethylphenyl)-1-(phenylcarbonylethyl)-1,2,3,6-tetrahydropyridine,

4-(4-methylphenyl)-1-((4-ethylphenyl)carbonylethyl)-1,2,3,6--tetrahydropyridine,

4-(4-fluorophenyl)-1-((4-chlorophenyl)carbonylethyl)-1,2,3,6-tetrahydropyridine,

4-(4-chlorophenyl)-1-(phenylcarbonylmethyl)-1,2,3,6-tetrahydropyridine or a pharmaceutically acceptable acid addition salt thereof.

5. Process for the preparation of a new tetrahydropyridine derivate of the formula (I)



(I)

in which

Ar^1 means a phenyl group optionally mono- or polysubstituted,

Ar^2 means a phenyl group optionally substituted,

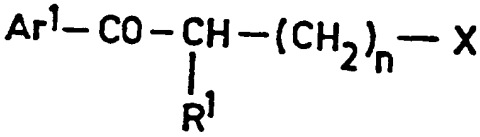
R^1 means a hydrogen atom or an alkyl group with 1-6 carbon atoms,

n can be either 0 or 1 with the proviso that if n = 0 then

R^1 can only mean a hydrogen atom and Ar^2 is in any case substituted

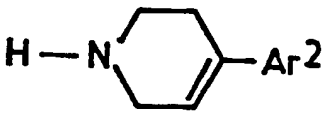
and acid addition salts thereof characterized in that

a) a ketone of the formula (II)



(II)

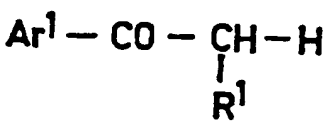
in which Ar^1, R^1 and n are as defined above and X means a halogen atom, is reacted with a substituted tetrahydropyridine derivative of the formula (III)



(III)

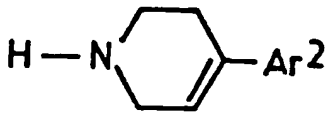
in which Ar^2 is as defined above, or

b) a ketone of the formula (IV),



(IV)

in which Ar^1 and R^1 are as defined above, is reacted with a tetrahydropyridine derivative of the formula (III),



(III)

in which Ar^2 is as defined above, or its salt and formaldehyde or a formaldehyde source to obtain a compound of the formula (I) with n = 1,

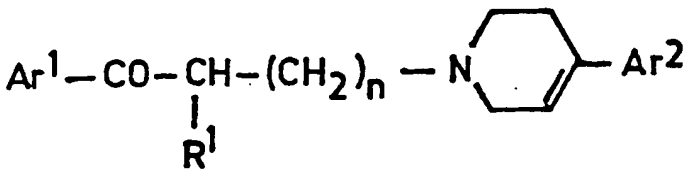
and, if desired, converting a compound of the formula (I), obtained by process a) or b) into an acid addition salt.

6. A process as claimed in variant a) or b) of claim 5, characterized by using a polar solvent, preferably an alkanol of 1-6 carbon atoms or a ketone.

7. A process as claimed in variant a) of claim 5, characterized by using as acid binding agent a tertiary amine with low number of carbon atoms, preferably trimethyl amine, or sodium acetate.

8. A process as claimed in variant b) of claim 5, characterized by using as formaldehyde source paraformaldehyde or dimethoxy methane.

9. Process for the preparation of pharmaceutical compositions, characterized by admixing a new tetrahydropyridine derivative of the formula (I)



(I)

in which

Ar^1 means a phenyl group optionally mono- or polysubstituted,

Ar^2 means a phenyl group optionally substituted,

R^1 means a hydrogen atom or an alkyl group with 1-6 carbon atoms,

n can be either 0 or 1 with the proviso that if n = 0 then R^1 can only mean a hydrogen atom and Ar^2 is in any case substituted

or a pharmaceutically acceptable acid addition salt thereof to auxiliary agents.

10. A process as claimed in claim 5, characterized by using as active agent

4-(4-chlorophenyl)-1-((4-chlorophenyl)carbonylethyl)-1,2,3,6-tetrahydropyridine,

4-(4-chlorophenyl)-1-((3,4,5-trimethoxyphenyl)carbonylethyl)-1,2,3,6-tetrahydropyridine,

4-(3-trifluoromethylphenyl)-1-((4-ethylphenyl)carbonylethyl)-1,2,3,6-tetrahydropyridine,

4-(3-trifluoromethylphenyl)-1-((4-fluorophenyl)carbonylethyl)-1,2,3,6-tetrahydropyridine,

4-(3-trifluoromethylphenyl)-1-(phenylcarbonylethyl)-1,2,3,6-tetrahydropyridine,

4-(4-methylphenyl)-1-((4-ethylphenyl)carbonylethyl)-1,2,3,6-tetrahydropyridine,

4-(4-fluorophenyl)-1-((4-chlorophenyl)carbonylethyl)-1,2,3,6-tetrahydropyridiine,

4-(4-chlorophenyl)-1-(phenylcarbonylmethyl)-1,2,3,6-tetrahydropyridine

or an acid addition salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 90/00076

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[5]: C 07 D 211/70; A 61 K 31/44

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
Int. Cl.[5]:	C 07 D 211/70

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

AT

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	GB, A, 948 071 (MAY & BAKER LIMITED) 29 January 1964 (29.01.64), see claims 1,8,15; page 1, lines 14-53.	(1,3,5)
A	GB, A, 1 246 656 (A.H. ROBINS COMPANY) 15 September 1971 (15.09.71), see claims 1,16,17.	(1,3)

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28 January 1991 (28.01.91)	07 February 1991 (07.02.91)
International Searching Authority	**Signature of Authorized Officer**
AUSTRIAN PATENT OFFICE	

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

Annex to the International Search Report on International Patent Application No. PCT/HU 90/00076

Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned International search report. The Austrian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche internationale visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office autrichien des brevets.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
GB-A - 948071		None	
GB-A - 1246656	15-09-71	CH-A - 554337	30-09-74
		DE-A - 1814342	23-10-69
		FR-A - 1597811	29-06-70
		JP-B4-51013157	26-04-76
		US-A - 3523950	11-08-70